Trafficking by GABARAP produces “super” $GABA_A$ channels

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γ-amino-butyric acid type A receptors ($GABA_AR$) are Cl^--selective ion channels whose function in the central nervous system is to control neuronal excitability. These receptors are the target of many prescribed drugs such as general anaesthetics (isoflurane), tranquillisers (valium), anti-epileptics (phenobarbitone), barbiturates (pentobarbital) and, also, are affected by alcohol. Very little is known about how any of these drugs affect these receptors and indeed, how GABA itself activates them. While fast synaptic transmission is inhibited by $GABA_A$ receptors at synapses, a steady tonic inhibitory signal is generated by $GABA_A$ receptors located at other sites on the neuronal cell body. It is proposed that it is these extrasynaptic receptors that are the principle target of drugs with chronic action, e.g., for modulation by tranquillisers and general anaesthetics. We have discovered that extrasynaptic $GABA_A$ channels in cultured neurons behave differently from those expressed in recombinant systems. $GABA_A$ channels in neurons exhibit a wide range of conductances and drugs increase both conductance and open probability. By contrast, recombinant $GABA_A$Rs neither display high conductance $GABA_A$ channels, nor do drugs increase their conductance, only open probability. Strikingly, we have been able to mimic the behaviour exhibited by neuronal extrasynaptic $GABA_A$Rs in a recombinant system and change the dispersion of the receptors in the membrane simply by co-expressing the trafficking protein GABARAP with $GABA_A$Rs. Our recent analysis of single channel properties of $GABA_A$Rs co-expressed with the trafficking protein GABARAP show that, in addition to drugs, GABA itself is also able to increase both the conductance and mean open time of channels. GABARAP increases the number of receptors in patches but the data suggest that it is having an additional effect, which we infer, is clustering, from immunofluorescence. Hence, clustering by GABARAP produces “super” $GABA_A$ channels.